

STANFORD UNIVERSITY  
STANFORD, CALIFORNIA

Kornberg

DEPARTMENT OF GENETICS  
School of Medicine

March 28, 1959

Dear Arthur:

I hope you won't have to spend much time answering this letter-- a few words will do.

How close are you to getting DNA synthesis from individual molecules of primer? It should be possible, ultimately, to 'plate out' single DNA molecules so as to get clones from them, assuming we can superimpose some mechanism for dissociating the immediate products of condensation so these can more effectively act as new primers. Your ~~poly-AT~~ poly-AT, as you point out, may well have ~~started~~ started out this way, being subject to very strong selection for species lacking G and C.

It strikes me then that a general method for getting other homogeneous species of DNA, of greater complexity than poly-AT, would be equivalent to clonal isolation by dilution: i.e., setting up a series of reaction ~~tubes~~ tubes with all four triphosphates, and progressive dilutions of a DNA primer. At some critical dilution, if you are lucky, you should run into tubes that show substantial (and self-accelerating) condensation after appreciable delay, i.e., comparable to the first appearance of poly-AT, but perhaps containing other more complex ~~products~~ products with characteristic base ratios. Of course the contaminating nucleases, as usual, cause all the trouble, and may make this experiment quite unrealistic. But I wonder if you can report any experience under conditions where the amount of DNA primer was critical.

Is there any point trying to set up systems where the nucleases are momentarily blocked by excess neutral DNA or RNA, or does this not work?

What these questions boil down to, Art, is that I feel quite inhibited about planning to set up any other new programs of genetic analysis when the treatment of molecules is so tantalizingly near by. The alternative to think about is artificial systems of molecular replication, like the mixed cation-anion ~~poly-~~ polymers I talked with you about: I've had a little encouragement on doing something about this with Frank Mayo, who used to be ~~at~~ at GE and is now at Stanford Research Institute, and one of the few traditional polymer chemists in the area. The catch is, there are strong hints that some of ~~the~~ the commercial labs. may already be on to the same game, viz. for condensations oriented by ~~complementary-ion~~ complementary-ion adsorption/ of the monomers.

Yours,

Joshua Lederberg

not sent  
sent 6/59